



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: G01N 33/74, C07K 4/12, C07K 7/08	A3	(11) International Publication Number: WO 99/54728 (43) International Publication Date: 28 October 1999 (28.10.1999)
------------------------------------------------------------------------------------------	-----------	--------------------------------------------------------------------------------------------------------------------------------------

(21) International Application Number: PCT/US99/06664

(22) International Filing Date: 26 March 1999 (26.03.1999)

(30) Priority Data:

60/082,756 23 April 1998 (23.04.1998) US
60/099,656 09 September 1998 (09.09.1998) US
60/115,345 08 January 1999 (08.01.1999) US

(60) Parent Application or Grant

NOVALON PHARMACEUTICAL CORPORATION [/];
(). PAIGE, Lisa, A. [/]; (). HAMILTON, Paul, T. [/];
(). FOWLKES, Dana, M. [/]; (). BUEHRER, Benjamin [/];
(). BARNETT, Tom [/]; (). MCDONNELL, Donald, P. [/];
(). CHRISTENSEN, Dale, J. [/]; (). PAIGE, Lisa, A. [/];
(). HAMILTON, Paul, T. [/]; (). FOWLKES, Dana, M. [/];
(). BUEHRER, Benjamin [/]; (). BARNETT, Tom [/];
(). MCDONNELL, Donald, P. [/]; (). CHRISTENSEN, Dale, J.
[/]; (). COOPER, Iver, P. ; ().

Published

(54) Title: METHOD OF PREDICTING RECEPTOR MODULATING ACTIVITY

(54) Titre: METHODE PERMETTANT DE PREVOIR LA CAPACITE DE COMPOSES DE MODULER L'ACTIVITE BIOLOGIQUE
DE RECEPTEURS

(57) Abstract

The ability of a query compound to modulate the biological activity of a receptor in a multicellular organism is predicted on the basis of its interaction with that receptor in the presence of various member of a panel of BioKeys. The BioKeys are ligands, especially peptides or nucleic acids, known to modify the conformation of the receptor. This interaction data, known as a "fingerprint", is compared to the fingerprints for reference compounds with known biological activities mediated by that receptor. In the "molecular braille" (MB) embodiment of the present invention, the reference and test fingerprints are based on in vitro (cell-free) assays. In the "cellular-braille" (CB) embodiment of the present invention, the reference and test fingerprints are based on cellular assays (but not on assays of whole multicellular organisms, or their organs or tissues).

(57) Abrégé

La présente invention permet de prévoir l'aptitude d'un composé d'intérêt à moduler l'activité biologique d'un récepteur dans un organisme multicellulaire à partir de son interaction avec ledit récepteur en présence de divers membres d'un groupe de bio-clés. Les bio-clés sont des ligands, en particulier des peptides ou des acides nucléiques, connus pour modifier la conformation du récepteur. Ces données d'interaction constituent ce que l'on appelle une "empreinte digitale", qui est comparée aux empreintes de composés de référence aux activités biologiques connues et dont le récepteur assure la médiation. Dans la réalisation dite "en braille moléculaire" de la présente invention, les empreintes digitales de référence et de test sont basées sur des essais in vitro (acellulaires). Dans la réalisation dite "en braille cellulaire" de la présente invention, les empreintes digitales de référence et de test sont basées sur des essais cellulaires (mais non pas sur des essais d'organismes multicellulaires complets, ou de leurs organes ou tissus).

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

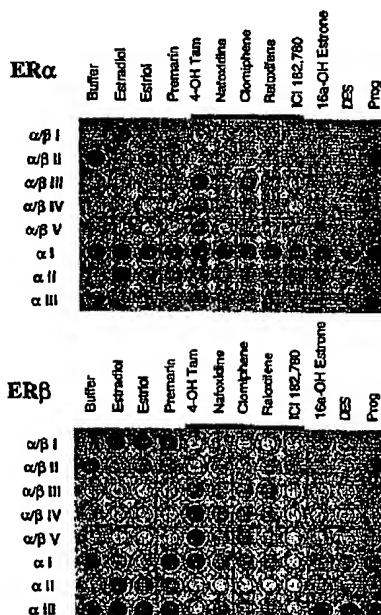
(51) International Patent Classification ⁶ : G01N 33/74, C07K 7/08, 4/12		A3	(11) International Publication Number: WO 99/54728
			(43) International Publication Date: 28 October 1999 (28.10.99)
(21) International Application Number: PCT/US99/06664			
(22) International Filing Date: 26 March 1999 (26.03.99)			
(30) Priority Data:			
60/082,756	23 April 1998 (23.04.98)	US	
60/099,656	9 September 1998 (09.09.98)	US	
60/115,345	8 January 1999 (08.01.99)	US	
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application			
US	Not furnished (CIP)		
Filed on	Not furnished		
(71) Applicant (for all designated States except US): NOVALON PHARMACEUTICAL CORPORATION [US/US]; Suite 560, 4222 Emperor Boulevard, Durham, NC 27703-8446 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): PAIGE, Lisa, A. [US/US]; 9414 Sawyer Road, Rougemont, NC 27572 (US). HAMILTON, Paul, T. [US/US]; 205 Muirwoods Drive, Cary, NC 27513 (US). FOWLKES, Dana, M. [US/US]; 2013 Damascus Church Road, Chapel Hill, NC 27516 (US). BUEHRER, Benjamin [US/US]; 5504 Garrett Road, Durham, NC 27707 (US). BARNETT, Tom [US/US]; 101 Barnehill Place, Chapel Hill, NC 27514 (US). MCDONNELL, Donald, P. [US/US]; Duke University Medical Center, Box 3813, Durham, NC 27710 (US). CHRISTENSEN, Dale, J. [US/US]; 226 Mint Hill Drive, Apex, NC 27502 (US).			
		(74) Agent: COOPER, Iver, P.; Browdy and Neimark, P.L.L.C., Suite 300, 419 Seventh Street N.W., Washington, DC 20004 (US).	
		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
		Published With international search report.	
		(88) Date of publication of the international search report: 10 February 2000 (10.02.00)	

(54) Title: METHOD OF PREDICTING RECEPTOR MODULATING ACTIVITY

(57) Abstract

The ability of a query compound to modulate the biological activity of a receptor in a multicellular organism is predicted on the basis of its interaction with that receptor in the presence of various member of a panel of BioKeys. The BioKeys are ligands, especially peptides or nucleic acids, known to modify the conformation of the receptor. This interaction data, known as a "fingerprint", is compared to the fingerprints for reference compounds with known biological activities mediated by that receptor. In the "molecular braille" (MB) embodiment of the present invention, the reference and test fingerprints are based on *in vitro* (cell-free) assays. In the "cellular-braille" (CB) embodiment of the present invention, the reference and test fingerprints are based on cellular assays (but not on assays of whole multicellular organisms, or their organs or tissues).

Different Ligands Induce Different Structural Alterations in ER α and ER β



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 99/06664A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/74 C07K7/08 C07K4/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 15586 A (TULARIK INC) 1 May 1997 (1997-05-01) the whole document ---	1-21
A	WO 97 31646 A (UNIV COLORADO) 4 September 1997 (1997-09-04) page 17, line 12 - line 18 page 32, line 1 - line 15 ---	1-21
A	MCDONNELL, D.P. ET AL.: "Analysis of Estrogen Receptor Function in Vitro Reveals Three Distinct Classes of Antiestrogens" MOLECULAR ENDOCRINOLOGY, vol. 9, no. 6, June 1995 (1995-06), pages 659-669, XP002113863 the whole document ---	1-21
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

1 September 1999

Date of mailing of the international search report

23. 11. 1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gundlach, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	NORRIS, JOHN D. ET AL: "Peptide antagonists of the human estrogen receptor" SCIENCE (WASHINGTON, D. C.) (1999), 285(5428), 744-746, XP002113864 the whole document	1-21
T	PAIGE, LISA A. ET AL: "Estrogen receptor (ER) modulators each induce distinct conformational changes in ER.alpha. and ER.beta." PROC. NATL. ACAD. SCI. U. S. A. (MARCH 1999), 96(7), 3999-4004, XP002113865 the whole document	1-21

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/06664

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-21

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-21

Characterization of substances having receptor-modulating activity

2. Claim : 22

Peptides that inhibit tamoxifen agonist activity comprising the general motif LXXLL

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/06664

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9715586 A	01-05-1997	AU 7457796 A	15-05-1997
WO 9731646 A	04-09-1997	AU 1975397 A	16-09-1997